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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/761,636	ACHEN ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,12,14-18,23-26,49-63 and 72-103* is/are pending in the application.

4a) Of the above claim(s) *4,14-17,25,56-62 and 89-103* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,12,18,23,24,26,49,51-53,63 and 72-88* is/are rejected.

7)☒ Claim(s) *50,54 and 55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-4, 12, 14-18, 23-26, 49-63, and 72-103 are pending.

2. Claims 4, 14-17, 25, 52, 56-62 and 89-103 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 1-3, 12, 18, 23-24, 26, 49-55, 63, and 72-88 are being acted upon in this Office Action.

4. In view of the amendment filed 6/25/04, the following rejections remain.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3, 12, 18, 23-24, 26, 63, and 72-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a monomeric monocyclic peptide which interferes with cell survival of at least one growth factor selected from the group consisting of VEGF, VEGF-C and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3, wherein the monomeric peptide consisting of SEQ ID NO: 5, 6, 7, 10, 11, 12, 13 and 14 for inhibiting VEGF-D induced VEGFR2 and VEGFR-3 mediated cell survival, **does not** reasonably provide enablement for (1) *all* monomeric monocyclic peptide which interferes with *all* biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3 wherein the monomeric monocycli peptide "comprises" *any* core sequence which consists of (a) binding-loop 1, 2 or 3 of VEGF-D as set forth in claims 1-3, and 72-88 (2) any monomeric, monocyclic peptide produced by a method comprising obtaining any "receptor-binding loop 1, 2 and 3 of VEGF-D", modified the loop with one or more "conservative amino acid substitution" to produce a modified loop as set forth in claims 12, 18, and 63, (3) a composition comprising said monomeric monocyclic peptide as set forth in claims 23-24 and 26. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only monomeric monocyclic peptides consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 5-7, and 10-14 derived from loop-1 or loop-2 of VEGF-D as shown in Figure 7 wherein the monomeric monocyclic peptide interferes with cell survival of least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.

The specification does not teach all monomeric monocyclic peptide "comprises" *any* core sequence which consists of (a) binding-loop 1, 2 or 3 of VEGF-D as set forth in claims 1-3, and 72-88 because there is insufficient guidance as to the structure of the "core sequence" of a receptor binding loop of 1, 2 or 3 of VEGF-D without the amino acid sequence. There is insufficient guidance as to which amino acids within the undisclosed core sequence of loop 1, 2 and/or 3 of VEGF-D to be substituted, deleted or inserted, much less the undisclosed fragment mimics a native conformation in the corresponding region of VEGF, VEGF-C or VEGF-D. Further, the term "comprising" is open-ended. It expands the monomeric monocyclic peptide to include additional amino acids at either or both ends. There is insufficient guidance as to which undisclosed amino acids to be added in addition to the problem of the core sequence.

Likewise, there is insufficient guidance in the specification as filed as how to obtain receptor-binding loop 1, 2 or 3 or the corresponding loop fragment that mimics a native conformation in the corresponding region of VEGF, VEGF-C or VEGF-D without the amino acid sequence in claim 12. Until the core sequence of the loop itself is enabled, the specification merely invites one of skilled in the art to further experimentation to arrive at the claimed invention. Given the infinite number of monomeric monocyclic peptide and biological activity,

there is insufficient working examples demonstrating that all monomeric monocyclic peptides could interfere with all biological activity of all VEGF such as VEGF, VEGF-C and VEGF-D mediated by at least one receptor such as VEGF receptor-2 and/or VEGF receptor-3.

It has been known in the art that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) is not well understood and is not predictable (e.g. see Ngo et al in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.).

Walsh *et al* teach that none of the available secondary structure predictors is able to predict accurately the secondary structure, and are not useful guides to designing peptides, let alone tertiary structure of the cysteine knot growth factors which the VEGF is a member (See page 395, in particular).

Kiba *et al* teach that a single loop of VEGF-A is not enough to be biologically functional. A pair of loop 1 and 3 of VEGF0ENZ-7 or VEGF-A may be required to build up the receptor binding for VEGFR-2 while loop 2 exchanges has no effect (See page 13461, column 1, second paragraph, in particular). Kiba *et al* further teach that even exchanging a region of VEGFA such as loop-3 with that of PIGF (member of the cysteine knot family) resulted with significant reduction in VEGFR-2 binding. However, its activity in inducing vascular permeability was still functional depending upon which bioassay (See page 13461, column 1, second paragraph, in particular).

Stacker *et al* teach that substituting amino acids 83-89 of VEGF with the analogous region of the related placenta growth factor (another member of the cysteine knot family) resulted in reduced VEGFR2 binding but retains the ability to induce vascular permeability using the Miles assay (See abstract, in particular).

Baldwin *et al* teach that receptor binding by VEGF-D is different in mouse and man (See entire document, abstract, in particular).

Attwood *et al*, of record, teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable.

Skolnick *et al,* of record, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular). It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or

compositions could result in substantially different pharmacological activities. In fact, Table 2 of the specification shows that not all monomeric monocyclic peptides are created equal and demonstrate to have the desired inhibitory activity. Even if the monomeric monocyclic peptides limited to those shown in Table 2, there is no in vivo working example in the specification as filed to support that any monomeric monocyclic peptides mentioned above would interfere with all biological activity of factor selected from the group consisting of VEGF, VEGF-C, ad VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.

Since the monomeric monocyclic peptides mentioned above are not enabled, it follows that all composition comprising said monomeric monocyclic peptides and at least one pharmaceutical carrier or adjuvant are not enabled (claims 22-24 and 26).

It also follows that any monomeric monocyclic peptide wherein the constraint maintains a beta-beta carbon separation distinct between opposing anti-parallel strands of any loop or any loop fragment at less than 6 angstrom is not enable because the term "comprises" is open-ended. There is insufficient guidance as how to maintain distinct between opposing anti-parallel strands of any loop or any loop fragment at less than 6 angstrom having additional undisclosed amino acids residues. With regard to claim 73, term "comprises" is open-ended. It expands the linking group to include additional carbon atoms at either or both ends to infinity, let alone the linking group having extra undisclosed heteroatoms, straight chain, branched and containing one or more of any saturated, unsaturated or aromatic ring. Since any undisclosed monomeric monocyclic peptide mentioned above are not enabled, it follows that any monomeric monocyclic peptide wherein the hetero atom such as the ones recited in claim 74, any constraint such as the ones recited in claims 75-82, 84 and 88 are not enabled. It also follows any residues contributing to any said chains of any undisclosed monomeric monocyclic peptide mentioned above such as the ones recited in claims 83 and 85 are not enabled.

For these reasons, it would require undue experimentation for one even skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of

the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 6/25/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) Claim 1 has been amended to recite a monomeric monocyclic peptide based on a core sequence that consists of a receptor binding loop of VEGF-D. (2) In continuing to reject the claims, manifests misunderstandings of the how and the scope of the claims. First, in the second full paragraph on Page 3, the Office Action continues to focus on specific examples of peptides that did not show inhibitory activity. These non-inhibitory peptides, however, are OUTSIDE the scope of the claims. They are disclosed in the specification to demonstrate that it is easy and routine to screen for monocyclic peptides that actually show inhibitory effect. Furthermore, it is improper to state that some of the exemplified dimeric peptides are not more effective than some monomeric peptides, because the law does not require an invention to be more effective to be enabled. (3) The paragraph bridging pages 3 and 4 of the Office Action discusses "insufficient guidance" for a relationship between peptide structure and function. This is improper because as long as an ordinarily skilled person can practice (make or use) the claimed invention, it is irrelevant whether the mechanism or underlining principle of the invention is known or understood. The core sequence of VEGF-D receptor binding loop 1, 2 ,3 are very short (about 15 amino acid long). Conservative substitution or deletion of such a short peptides, coupled with well-known screening methods, requires only limited amount of effort for an ordinarily skilled artisan to make and use the invention as claimed, i.e. to obtain inhibitory monocyclic peptides. The claimed peptide comprises a core whose length and structure is finite and well-defined. The law does not require in vivo data for a patent claim to be allowable. See e.g. In re Brana 51 F.3d 1560, 1566 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications). (4) The Office Action seems to be extremely concerned with the use of the term "comprising," because a discussion thereof is repeated in the first full paragraph on Page 6 (and many times in subsequent parts of the Office Action). Applicants respectfully submit that the fact that it is open ended does not make a claim non-enabled. The legal standard is whether an ordinarily skilled person would be able to practice the claimed invention without undue experimentation, not whether the claim may theoretically encompass some extreme and non functional "embodiments." For example, if a specification discloses a novel active pharmaceutical ingredient X, a claim of a pharmaceutical composition

comprising X and a suitable carrier" is enabled, even though the claim is open ended and theoretically encompasses a composition that also contains extremely toxic amount of arsenic. To an ordinarily skilled person in the relevant art, there is no need to engage in undue experimentation to practice the claimed invention. The fixation of the office action on an indefinite" number of amino acids that may theoretically be added to the loop (after it is circulized) is similarly misplaced and improper.

In response, the specification does not define the "core sequence" of loop 1, loop 2, and loop 3 of all VEGF-D such as human VEGF-D without the amino acid sequence, much less about the corresponding loop fragment that mimics a native conformation in the corresponding region of all VEGF, VEGF-C or VEGF-D. The specification discloses only monomeric monocyclic peptides consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 5-7, and 10-14 derived from loop-1 or loop-2 of VEGF-D as shown in Figure 7 wherein the monomeric monocyclic peptides interferes with cell survival of least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.

The specification discloses only monomeric monocyclic peptides consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 5-7, and 10-14 derived from loop-1 or loop-2 of VEGF-D as shown in Figure 7 wherein the monomeric monocyclic peptide interferes with cell survival of least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.

The specification does not teach all monomeric monocyclic peptide "comprises" *any* core sequence which consists of (a) binding-loop 1, 2 or 3 of VEGF-D as set forth in claims 1-3, and 72-88 because there is insufficient guidance as to the structure of the "core sequence" of a receptor binding loop of 1, 2 or 3 of VEGF-D without the amino acid sequence. There is insufficient guidance as to which amino acids within the undisclosed core sequence of loop 1, 2 and/or 3 of VEGF-D to be substituted, deleted or inserted, much less the undisclosed fragment mimics a native conformation in the corresponding region of VEGF, VEGF-C or VEGF-D. Further, the term "comprising" is open-ended. It expands the monomeric monocyclic peptide to include additional amino acids at either or both ends. There is insufficient guidance as to which undisclosed amino acids to be added in addition to the problem of the core sequence.

Likewise, there is insufficient guidance in the specification as filed as how to obtain receptor-binding loop 1, 2 or 3 or the corresponding loop fragment that mimics a native conformation in the corresponding region of VEGF, VEGF-C or VEGF-D without the amino acid sequence in claim 12. Until the core sequence of the loop itself is enabled, the specification merely invites one of skilled in the art to further experimentation to arrive at the claimed invention. Given the infinite number of monomeric monocyclic peptide and biological activity, there is insufficient working examples demonstrating that all monomeric monocyclic peptides could interfere with all biological activity of all VEGF such as VEGF, VEGF-C and VEGF-D mediated by at least one receptor such as VEGF receptor-2 and/or VEGF receptor-3. Applicant is directed to the detail explanation above.

7. Claims 1-3, 12, 18, 23-24, 26, 63, and 72-88 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *all* monomeric monocyclic peptide which interferes with *all* biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3 wherein the monomeric monocycli peptide "comprises" *any* core sequence which consists of (a) binding-loop 1, 2 or 3 of *all* VEGF-D as set forth in claims 1-3, and 72-88, (2) any monomeric, monocyclic peptide produced by a method comprising obtaining any "receptor-binding loop 1, 2 and 3" of *all* VEGF-D, modified the loop with one or more "conservative amino acid substitution" to produce a modified loop as set forth in claims 12, 18, and 63, and (3) a composition comprising said monomeric monocyclic peptide as set forth in claims 23-24 and 26.

The specification discloses only monomeric monocyclic peptides consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 5-7, and 10-14 derived from loop-1 or loop-2 of VEGF-D as shown in Figure 7 wherein the monomeric monocyclic peptide interferes with cell survival of least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.

Other than the specific monocyclic monomeric peptide consisting of SEQ ID NO: 5, 6, 7, 10, 11, 12, 13 and 14, there is inadequate written description about the structure associated with function of *any* "core sequence", *any* "receptor binding loop 1, 2, or 3" of all VEGF, all VEGF-C and all VEGF-D without the amino acid sequence, much less which amino acids within the undisclosed core sequence consists of loop 1, 2 and/or 3 of VEGF-D to be substituted, deleted or inserted. Further, the term "comprising" in claim 1 is open ended. It expands the monomeric monocyclic peptide to include additional amino acids at either or both ends. There is inadequate written description about which undisclosed amino acids to be added in addition to the undisclosed core sequence or receptor binding loop 1, 2 or 3 of VEGF-D. Since the monomeric monocyclic peptides mentioned above are not adequately described, it follows that all composition comprising all undisclosed monomeric monocyclic peptides and at least one pharmaceutical carrier or adjuvant are not adequately described.

Further, there is inadequate written description about which amino acid within the undisclosed "core sequence consists of receptor binding loop 1, 2 or 3 of VEGF-D" to be substitute, deleted, or inserted while which activity is retained or interferes by which receptor. In addition to the lack of a written description for "core sequence" mentioned above, the term "comprising" is open-ended. It expands the undisclosed "core sequence" having one or more amino acid substitution, or one or more amino acids deletion or insertion to include additional amino acids at either or both ends. There is insufficient written description about undisclosed amino acids to be added and retains the desired activity mediated by the specific VEGF receptor. Given the core sequence of the loop 1, 2 or 3 *all* VEGF-D of the monomeric monocyclic peptides are not adequately described, it follows that the amino acids within the loops or core sequence mentioned above comprising the extra undisclosed amino acid residues to be substituted, deleted and/or added are not adequately described. It also follows that any composition comprising any undisclosed monomeric monocyclic peptides are not adequately described. Because the primary structure of the core sequence has not been described, the tertiary structure of any monomeric monocyclic peptide wherein the constraint maintains a beta-beta carbon separation distinct between opposing anti-parallel strands of any loop or any loop fragment at less than 6 angstrom is not adequately described. Further, the term "comprises" is open-ended. It expands the linking group to include additional atoms, or heteroatoms (claim 73) to include additional amino acid residues or carbon atoms at either or both ends. There is a lack of written description about which undisclosed atoms or amino acids to be included while maintains VEGF receptors binding

and interferes with all its biological activity. Since any of the undisclosed monomeric monocyclic peptide mentioned above are not adequately described, it follows that any monomeric monocyclic peptide wherein the hetero atom such as the ones recited in claim 74, any constraint such as the ones recited in claims 75-82, 84 and 88 are not adequately described. It also follows any residues contributing to any said chains of any undisclosed monomeric monocyclic peptide mentioned above such as the ones recited in claims 83 and 85 are not adequately described. It also follows that any composition comprising the undisclosed monomeric monocyclic peptide are not adequately described.

The specification discloses only the specific monomeric monocyclic peptides derived from only *human* VEGF-D, all other monomeric monocyclic peptide comprises a core sequence which consists of a receptor-binding loop 1, 2 or 3 of all VEGF-D with one or more conservative amino acid substitution, or with one or more amino acid residues deleted or inserted that mimics a native conformation in the corresponding VEGF, or VEGF-C are not adequately described. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of functional monomeric monocyclic peptide to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 6/25/04 have been fully considered but are not found persuasive.

Applicants' position is that the rejection related to the recitation of "loop 1, 2, and 3 of VEGF, and VEGF-C" (including the new matter" rejection has been obviated by the above claim amendments. It is believed that the amendments.

In response to Applicants' arguments, the specification discloses only monomeric monocyclic peptides consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 5-7, and 10-14 derived from loop-1 or loop-2 of VEGF-D as shown in Figure 7 wherein the monomeric monocyclic peptide interferes with cell survival of least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.

Other than the specific monocyclic monomeric peptide consisting of SEQ ID NO: 5, 6, 7, 10, 11, 12, 13 and 14, there is inadequate written description about the structure associated with function of *any* "core sequence", *any* "receptor binding loop 1, 2, or 3" of all VEGF, all VEGF-C and all VEGF-D without the amino acid sequence, much less which amino acids within the undisclosed core sequence consists of loop 1, 2 and/or 3 of VEGF-D to be substituted, deleted or inserted. Further, the term "comprising" in claim 1 is open ended. It expands the monomeric monocyclic peptide to include additional amino acids at either or both ends. There is inadequate written description about which undisclosed amino acids to be added in addition to the undisclosed core sequence or receptor binding loop 1, 2 or 3 of VEGF-D. Since the monomeric monocyclic peptides mentioned above are not adequately described, it follows that all composition comprising all undisclosed monomeric monocyclic peptides and at least one pharmaceutical carrier or adjuvant are not adequately described.

8. The following new grounds of rejections are necessitated by the amendment filed 6/25/04.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-3, 23, and 72-87 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

"A monomeric monocyclic peptide..... a core sequence which consists of (a) a receptor-binding loop 1, 2 or 3 of VEGF-D...the corresponding loop fragment **mimics a native conformation in the corresponding region of VEGF, VEGF-C**" in claim 1 represents a departure from the specification and the claims as originally filed because said phrase has no support in the claims and the specification as originally filed. There is a lack of a written support in the specification for monomeric monocyclic peptide derived from the receptor binding loop 1, 2 or 3 of VEGF-D mimics the native conformation of the undisclosed VEGF and VEGF-C. Applicant's response filed 6/25/04 fails to point out the support for the phrase.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 49, and 52-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamada *et al* (Genomics 42(3):483-8; June 15, 1997; PTO 892).

Yamada *et al* teach various cyclic peptides such as human VEGF-D comprising CNEESLIC (See Figure 1, "*" at residues 147 to 154 of human VEGF-D, in particular) or CSPRETCVEVASELGKSINTFFKPPC (See Figure 1, first "*" to second "*", in particular). The reference peptide having cysteine residues at the N-terminal and C terminal inherently forms disulfide bond to form a cyclic structure. Further, the term "comprising" is open-ended. It expands the claimed SEQ ID NO: 6 or SEQ ID NO: 5 to include additional amino acids residues at either or both ends to include the reference peptides. Thus, the reference teachings anticipate the claimed invention.

14. Claims 49, and 51-53 are rejected under 35 U.S.C. 102(e) as being anticipated by Achen *et al* (US Pat No 6,383,484 filed Dec 21, 1999; PTO 892).

The '484 patent teaches a cyclic peptide such as human VEGF-D comprising SEQ ID NO: 1. The reference cyclic peptide Ala Ser Glu Leu Gly Lys Ser Thr Asn Thr Phe Phe Lys Pro Pro Cys includes the claimed peptide SEQ ID NO: 5 (See residues 29-39 of SEQ ID NO: 1, in particular). The reference cyclic peptide Cys Cys Asn Glu Glu Ser Leu Ile Cys includes the claimed peptide of SEQ ID NO : 6 (See residues 33 or 34 to 61 of SEQ ID NO: 1, in particular).

The term "comprising" is open-ended. It expands the claimed cyclic peptides to include additional amino acids at either or both ends to include the reference peptides. The reference peptide having cysteine residues at the N-terminal and C terminal inherently forms disulfide bond to form a cyclic structure. The reference peptides inherently interfere with a biological activity such as proliferation of endothelial cell mediated by VEGF receptor 2 or VEGF receptor 3. Thus, the reference teachings anticipate the claimed invention.

15. Claim 49 is rejected under 35 U.S.C. 102(b) as being anticipated by Le et al (Accession No. T25674, Oct 1999; PTO 892).

Le et al teach a cyclic peptide comprising CVPLTC of claimed SEQ ID NO: 12. The term "comprising" is open-ended. It expands the claimed cyclic peptide to include additional amino acids at either or both ends to include the reference peptide. The reference peptide having cysteine residues at the N-terminal and C terminal inherently forms disulfide bond to form a cyclic structure. Thus, the reference teachings anticipate the claimed invention.

16. Claims 50 and 54-55 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

17. SEQ ID NO: 10-11 and 13-14 are free of prior art.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

20. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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September 17, 2004

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